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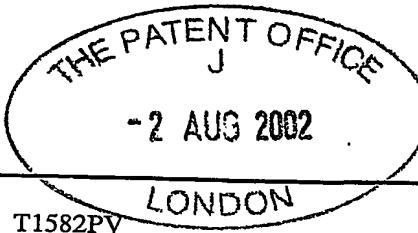


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1/77

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Title of the invention

0218041.2

05AUG02 E736317 1 002637
P01/7700 0.00-0218041.2

02 AUG 2002

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Name of your agent (if you have one)

Mr. J. Horgan

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Patents ADP number (if you know it)

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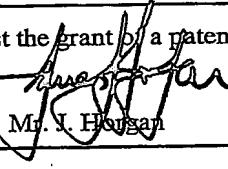
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1.

I/We request the grant of a patent on the basis of this application.

Signature



Date 02 August, 2002

Mr. J. Horgan

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Mr. J. Horgan

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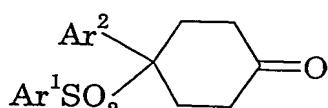
CHEMICAL PROCESS

This invention is in the field of synthetic organic chemistry, and in particular concerns a novel synthetic route to a particular class of 4,4-disubstituted cyclohexanones which have useful therapeutic properties, and which are key intermediates in the synthesis of further compounds having therapeutic properties.

As disclosed in our copending International Patent Application No. PCT/GB01/03741, filed 21st August 2001, a particular class of cyclohexane derivatives have been found to have activity as modulators of the processing of amyloid precursor protein (APP) by γ -secretase into the β -amyloid peptide. Since the secretion of β -amyloid is believed to play a primary role in the onset and progression of Alzheimer's disease, the said cyclohexane derivatives are useful in the treatment and/or prevention of Alzheimer's disease.

Included within the aforementioned class of cyclohexane derivatives are cyclohexanones in which the carbon atom in the 4-position is bonded to an aryl or heteroaryl group and also to an arylsulphonyl or heteroarylsulphonyl group. Furthermore, said cyclohexanones are key intermediates in the synthesis of other members of the aforementioned class of cyclohexane derivatives, notably the corresponding 4,4-disubstituted cyclohexanopropanoic acids, and esters and amides derived therefrom. There is therefore a need for an efficient synthesis of said cyclohexanones and cyclohexanopropanoic acids, amenable to execution on a large scale.

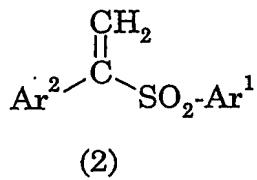
According to the present invention, there is provided a method of preparing a cyclohexanone of formula (1):



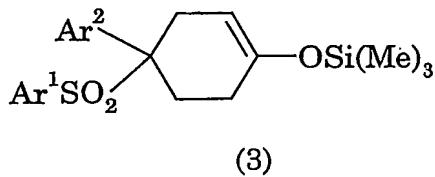
(1)

comprising:

(a) cycloaddition of 2-trimethylsilyloxybutadiene to a vinyl derivative of formula (2):



5 to form a silyl enol ether of formula (3):



and

(b) hydrolysis of said silyl enol ether to form the cyclohexanone of formula (1);

10 wherein, in each of formulae (1), (2) and (3), Ar^1 represents $\text{C}_{6-10}\text{aryl}$ or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2 , CF_3 , OH, OCF_3 , $\text{C}_{1-4}\text{alkoxy}$ or $\text{C}_{1-4}\text{alkyl}$ which optionally bears a substituent selected from halogen, CN, NO_2 , CF_3 , OH and $\text{C}_{1-4}\text{alkoxy}$; and

15 Ar^2 represents $\text{C}_{6-10}\text{aryl}$ or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2 , CF_3 , OH, OCF_3 , $\text{C}_{1-4}\text{alkoxy}$ or $\text{C}_{1-4}\text{alkyl}$ which optionally bears a substituent selected from halogen, CN, NO_2 , CF_3 , OH and $\text{C}_{1-4}\text{alkoxy}$.

20 Preferably, Ar^1 represents phenyl or heteroaryl, optionally substituted as indicated above. Typical heteroaryl embodiments of Ar^1 include optionally substituted pyridyl, in particular optionally substituted 3-pyridyl. Preferably, Ar^1 bears 0-2 substituents, more preferably 1 or 2 substituents, and most preferably 1 substituent which is preferably in the *para*-position relative to the sulphone group. Typical substituents include halogen (especially chlorine, bromine and fluorine), $\text{C}_{1-4}\text{alkyl}$ (such as methyl), $\text{C}_{1-4}\text{alkoxy}$ (such as methoxy), and CF_3 . Examples of groups

represented by Ar¹ include 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 4-methoxyphenyl, 6-trifluoromethylpyrid-3-yl and 6-chloropyrid-3-yl. Most preferably, Ar¹ represents 4-chlorophenyl, 4-trifluoromethylphenyl or 6-trifluoromethylpyrid-3-yl.

Preferably, Ar² represents phenyl bearing 1, 2 or 3 substituents as indicated, and most preferably, Ar² represents 2,5-disubstituted phenyl or 2,3,6-trisubstituted phenyl. Preferred substituents include halogen (especially bromine, chlorine and fluorine), nitrile and substituted alkyl, such as hydroxymethyl. Examples of groups represented by Ar² include 2,5-dichlorophenyl, 2,5-difluorophenyl, 2-bromo-5-fluorophenyl, 5-bromo-2-fluorophenyl, 5-iodo-2-fluorophenyl, 2-hydroxymethyl-5-fluorophenyl, 5-cyano-2-fluorophenyl and 2,3,6-trifluorophenyl. Most preferably, Ar² represents 2,5-difluorophenyl or 2,3,6-trifluorophenyl.

In a preferred embodiment, Ar¹ represents 4-chlorophenyl and Ar² represents 2,5-difluorophenyl.

In step (a), the cycloaddition reaction between the vinyl derivative (2) and 2-trimethylsilyloxybutadiene to form silyl enol ether (3) may be carried out at elevated temperatures (e.g. 50 – 200°C, preferably 100 – 150°C) in an inert solvent, especially a hydrocarbon solvent, preferably under an inert atmosphere. A preferred solvent is *m*-xylene. An excess of 2-trimethylsilyloxybutadiene, e.g. of about 2-fold, may be used. In a typical procedure in accordance with the invention, the vinyl derivative (2) is reacted with a 2-fold molar excess of 2-trimethylsilyloxybutadiene in *m*-xylene at 130°C under nitrogen for a period of 5 to 50 hours, typically 10 to 30 hours, and preferably about 26 hours.

In step (b), the hydrolysis of the silyl enol ether (3) to the cyclohexanone (1) is typically carried out by treatment with aqueous mineral acid at ambient or moderately elevated temperature, e.g. in the range 20 – 100°C, preferably 30 – 80°C). Most advantageously, the hydrolysis is carried out *in situ* immediately after the cycloaddition

reaction, without isolation or further purification of the silyl enol ether. In a typical procedure in accordance with the invention, the reaction mixture from step (a) is distilled under reduced pressure to remove residual diene with addition of solvent to maintain a constant volume, then diluted with 5 THF and stirred vigorously with aqueous mineral acid (e.g. 3M hydrochloric acid) at about 50°C. The hydrolysis is typically complete within one hour at this temperature.

10 The product cyclohexanone (1) may then be isolated by separating the organic layer, washing it with water, and removing most of the solvent by distillation at atmospheric pressure. In a typical procedure, the residue from the distillation is allowed to cool to about 75°C, then heptane is added slowly to facilitate crystallisation of the product, which may then be collected and dried in the conventional manner.

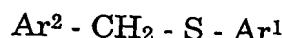
15 The vinyl derivatives (2) may be prepared from sulphones (4):

$$\text{Ar}^2 - \text{CH}_2 - \text{SO}_2 - \text{Ar}^1 \quad (4)$$

where Ar^1 and Ar^2 have the same meanings as before. For example, the sulphones (4) may be treated sequentially with butyllithium, trimethylsilyl chloride and formaldehyde in THF at -78°C to form (2). 20 Alternatively, the aforesaid treatment with butyllithium may be followed by quenching with N,N-dimethylmethylenammonium iodide and quaternisation of the resulting Mannich adduct with methyl iodide.

25 ~~Spontaneous elimination of trimethylamine during subsequent aqueous extractive work up then provides the vinyl derivatives (2). However, in a preferred route to vinyl derivatives (2), the sulphones (4) are reacted with N,N,N',N'-tetramethyldiaminomethane and acetic anhydride in DMF. In a typical process, the sulphone (4) is reacted with a 1.5- to 3-fold excess of the diamine and a 3- to 6-fold excess of acetic anhydride in DMF at about 60°C for 4 to 18 hours, followed by cooling and dilution with water to precipitate the product.~~

The sulphones (4) are available via oxidation of the corresponding thioethers (5):

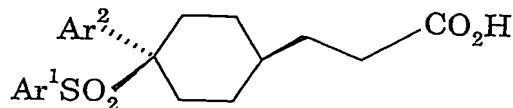


(5)

5 where Ar^1 and Ar^2 have the same meanings as before. A variety of oxidising agents may be used, such as hydrogen peroxide and peroxy acids, including *m*-chloroperoxybenzoic acid. In a preferred oxidative process, the thioether (5) is treated with hydrogen peroxide in a toluene-water biphasic system, in the presence of a sodium tungstate catalyst and a
10 quaternary ammonium salt phase transfer catalyst, such as Aliquat 336TM.

The thioethers (5) are available via reaction of thiols $\text{Ar}^1 - \text{SH}$ with $\text{Ar}^2 - \text{CH}_2 - \text{X}$, where Ar^1 and Ar^2 have the same meanings as before, and X is a leaving group, in particular halogen, preferably bromine or chlorine. The reaction takes place in the presence of base. In a preferred process,
15 the reaction is carried out in industrial methylated spirits at ambient temperature or below, using aqueous sodium hydroxide as base.

The cyclohexanones (1) have utility as modulators of the processing of amyloid precursor protein by gamma secretase, and hence are potentially suitable for the treatment or prevention of Alzheimer's disease.
20 Furthermore, chemical manipulation of the ketone group of the cyclohexanones (1) enables the synthesis a variety of compounds showing similar or greater potency towards gamma secretase, providing access to drug candidates with varying pharmacokinetic profiles. In particular, the cyclohexanones are precursors of cyclohexanepropanoic acids (6) and esters
25 and amides derived therefrom, which are disclosed in International Patent Application No. PCT/GB01/03741, filed 21st August 2001,



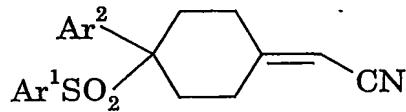
(6)

where Ar^1 and Ar^2 have the same meanings as before.

Accordingly, a preferred embodiment of the inventive process comprises the additional steps of:

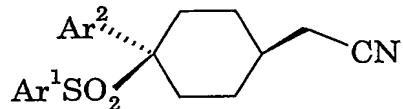
(c) reacting a cyclohexanone of formula (1) with a di(C₁₋₄alkyl) cyanomethylphosphonate and base to form a cyclohexylideneacetonitrile

5 (7):



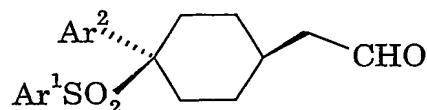
(7)

(d) reducing said cyclohexylideneacetonitrile with lithium tri-sec-butylborohydride to form the corresponding *cis* cyclohexaneacetonitrile (8):



(8)

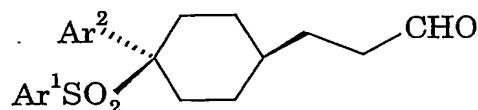
10 (e) sequential treatment of said *cis* cyclohexaneacetonitrile with diisobutylaluminium hydride and aqueous acid to form the corresponding *cis* cyclohexaneacetaldehyde (9):



(9)

(f) homologation of said *cis* cyclohexaneacetaldehyde to the

15 corresponding *cis* cyclohexanepropanal (10):



(10)

and

(g) oxidising said *cis* cyclohexanepropanal to the corresponding *cis* cyclohexanepropanoic acid (6);

wherein, in each of steps (c) to (g), Ar^1 and Ar^2 have the same meanings as before, and "cis" refers to the stereoconfiguration of the side chain relative to the Ar^1SO_2 group.

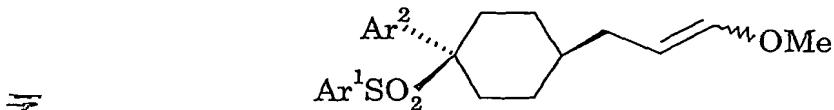
5 In step (c), the C_{1-4} alkyl groups are typically methyl or ethyl, preferably ethyl, and the reaction is typically carried out in THF at about -5°C using a strong base such as potassium *t*-butoxide.

In step (d), the reduction is typically carried out in THF at about -60°C .

10 In step (e), the reaction with diisobutylaluminium hydride is typically carried out at about -60°C in toluene, and the subsequent acid hydrolysis by stirring the resulting solution with aqueous acid (e.g. citric acid) at ambient temperature overnight.

15 In step (g), the oxidation is advantageously effected in a dichloromethane-water biphasic system at ambient temperature using an aqueous solution of sodium chlorite and sulphamic acid as oxidant.

20 In one embodiment, the homologation in step (f) is effected by reaction of the *cis* cyclohexaneacetaldehyde (9) with a methoxymethyltriphenylphosphonium salt (e.g. a halide, such as the chloride) and strong base, followed by hydrolysis of the resulting mixture of enol ethers (11):



(11)

25 with aqueous acid. Typically, the reaction is carried out in toluene at reduced temperature (e.g. $0 - 5^\circ\text{C}$) using potassium *t*-butoxide as the strong base. The intermediate enol ether may be hydrolysed in its crude form in a mixture of aqueous hydrochloric acid and DMF at moderately elevated temperature (e.g. about $40 - 50^\circ\text{C}$).

In an alternative embodiment, the homologation in step (f) is effected by reducing the cyclohexaneacetaldehyde (9) to the corresponding

cyclohexaneethanol (for example, using sodium borohydride in an ethanol/toluene mixture at about 4°C); converting same to a sulphonate ester such as the mesylate, tosylate or triflate (for example, by treatment with the appropriate sulphonyl chloride in dichloromethane in the presence of a tertiary amine at about -30°C); displacing the sulphonate group with cyanide to form the corresponding cyclohexanepropionitrile (for example, using potassium cyanide in DMSO solution at ambient temperature); then treating said cyclohexanepropionitrile sequentially with diisobutylaluminium hydride and aqueous acid to form the desired aldehyde (10) (for example, under the same conditions as in step (e)).

Using conventional coupling reactions, the acids (6) may be converted to the corresponding esters and/or amides disclosed in International Patent Application No. PCT/GB01/03741, filed 21st August 2001.

The above-described processes provide a convenient, economical route to the cyclohexanepropanoic acids of formula (6) which is suitable for execution on a multi-kilogram scale. Particularly noteworthy is the fact that the reduction in step (d) introduces the desired *cis* stereochemistry essentially quantitatively, thereby avoiding the need for a costly and time-consuming separation of *cis* and *trans* isomers.

Accordingly, the invention further provides a process for the synthesis of a cyclohexanepropanoic acid of formula (6) comprising the steps (c) – (g) detailed above.

The products of the novel processes disclosed herein have an activity as modulators of the processing of APP by γ secretase, and are therefore useful in the treatment or prevention of disorders involving excessive secretion and/or deposition of β -amyloid, in particular Alzheimer's disease.

For use in medicine, said products optionally may be in the form of pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds made by the process of this invention include acid addition salts, such as those formed with hydrochloric, sulphuric,

benzenesulphonic, methanesulphonic, fumaric, maleic, succinic, acetic, benzoic, oxalic, citric, tartaric, carbonic or phosphoric acids, and, where the compounds of the invention carry an acidic moiety, salts formed by neutralisation of said acidic moiety with a suitable base, such as sodium, 5 potassium, ammonium, calcium or magnesium salts, and salts formed with suitable organic ligands, e.g. amine salts; quaternary ammonium salts or pyridinium salts.

The products formed via the inventive process may be used to 10 prepare pharmaceutical compositions comprising one or more of the said products or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier. For use in said compositions, products of the inventive process which comprise a carboxylic acid group are preferably in the form of the free acid or the sodium salt thereof. Preferably these compositions are in unit dosage forms such as tablets, 15 pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid 20 compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, such as the conventional tableting ingredients known to those skilled in the art, e.g. as described in WO 01/70677, and formed into unit dosage forms. Typical unit dosage forms contain from 1 to 250 mg, for example 1, 2, 5, 10, 25, 50, 100, 200 or 250 mg, of the active 25 ingredient. Tablets or pills of the composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, as described, for example, in WO 01/70677.

The liquid forms in which the compositions may be incorporated for 30 administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils, as described in WO 01/70677.

For treating or preventing Alzheimer's disease, a suitable dosage level of the active ingredient is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.1 to 50 mg/kg of body weight per day. The compounds may be administered on a regimen of 5 1 to 4 times per day. In some cases, however, dosage outside these limits may be used.

Where the active ingredient is a carboxylic acid, it is preferably administered as the free acid or as the sodium salt thereof.

Assays for determining the level of activity of the relevant 10 compounds towards γ -secretase are disclosed in WO 01/70677 and in *Biochemistry*, 2000, 39(30), 8698-8704. See also, *J. Neuroscience Methods*, 2000, 102, 61-68.

EXAMPLES

15 Example 1

2-[[[4-chlorophenyl)thio]methyl]-1,4-difluorobenzene

4-Chlorothiophenol (253g, 1.75mol) was dissolved in industrial methylated spirits (1265mL) and 2M sodium hydroxide solution (901mL) was added, maintaining the temperature below 20°C. A solution of 2,5-difluorobenzyl bromide (355g, 1.72mol) in industrial methylated spirits (250mL) was added dropwise to the thiolate solution, maintaining the temperature below 15°C. Upon completion of the reaction, water (1000mL) was added. The resulting slurry was aged at 5°C and then filtered. The cake was washed sequentially with cold industrial methylated spirits : water (40:60) and then water (500mL). Drying *in vacuo* at ambient temperature furnished 2-[[[4-chlorophenyl)thio]methyl]-1,4-difluorobenzene (462.3g, 99.6%). ¹H NMR (CDCl₃) 7.23 (4H, s), 6.69-6.86 (3H, m) and 4.04 (2H, s).

30 Example 2

2-[[[4-chlorophenyl)sulfonyl]methyl]-1,4-difluorobenzene

A mixture of sodium tungstate dihydrate (1.83g, 5.54mmol) as a solution in water (36.56mL), 1M sulfuric acid (2.50mL), 2-[[¹⁸(4-chlorophenyl)thio]methyl]-1,4-difluorobenzene (Example 1) (100g, 0.37mol) and Aliquat 336TM (2.99g, 7.39mmol) in toluene (500mL) was heated to 5 45°C, and 27.5% aqueous hydrogen peroxide (114.2mL) was added slowly. The mixture was cooled and the unreacted peroxide was quenched by addition of 20wt% sodium metabisulfite solution (120mL). The layers were separated. The organic phase was washed with water (190mL) and concentrated to a total volume of approximately 200 mL. Heptane 10 (400mL) was added and the resulting mixture was cooled to 0°C and filtered. The wet cake was washed with 2:1 heptane:toluene (200mL) and then heptane (200mL). The product was dried *in vacuo* at 40°C to yield 107.6g of 2-[[¹⁸(4-chlorophenyl)sulfonyl]methyl]-1,4-difluorobenzene (96% yield). ¹H NMR CDCl₃ 7.61 (2H, d, J=8.6Hz), 7.45 (2H,d, J=8.6Hz), 7.13- 15 7.08 (1H, m), 7.05-7.00 (1H, m), 6.99-6.87 (1H, m) and 4.36 (2H, s).

Example 3

2-[1-[(4-chlorophenyl)sulfonyl]ethenyl]-1,4-difluorobenzene

2-[[¹⁸(4-chlorophenyl)sulfonyl]methyl]-1,4-difluorobenzene (Example 20 2) (100g, 0.33mol) and N,N,N',N'-tetramethyldiaminomethane (34.2g, 0.50mol) were dissolved in dimethyl formamide (1000mL) at 60°C. Acetic anhydride (68.3g, 1.00mol) was added slowly and the reaction mixture was aged for 5 hours. Water (1000 mL) was added dropwise and the resulting slurry was cooled to 5°C. The solids were filtered, and the cake washed 25 sequentially with dimethyl formamide:water (40:60, 200mL) and water (500mL). Drying overnight *in vacuo* at 40°C under a nitrogen stream furnished 2-[1-[(4-chlorophenyl)sulfonyl]ethenyl]-1,4-difluorobenzene (98g, 95%). ¹H NMR (CDCl₃) 7.64-7.59 (2H, m), 7.43-7.39 (2H, m), 7.27-7.22 (1H, m), 7.08-6.88 (2H, m), 6.88 (1H, s) and 6.09 (1H, s).

30

Example 4

4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone

A solution of 2-[1-[(4-chlorophenyl)sulfonyl]ethenyl]-1,4-difluorobenzene (Example 3) (100g, 0.32mol) in xylenes (500ml) was azeotropically distilled at 38°C, 20 mmHg, until 300mL solvent had been removed. 2-Trimethylsilyloxybutadiene (90.4 g, 0.64mol) was then added under a nitrogen atmosphere and the mixture heated to 130 °C. After the reaction was completed, the mixture was distilled *in vacuo* to remove residual diene, whilst maintaining a constant volume by the addition of xylenes (400 mL). The mixture was cooled to 50°C and THF (500 mL) and 3M HCl (424 mL, 1.27mol) were added. After the hydrolysis was complete, the layers were separated. The organic layer was washed with water (300 mL) and then concentrated by atmospheric distillation until 350 mL of solvent had been removed. The solution was allowed to cool until crystallisation started, heptane (600mL) was added and the resulting mixture cooled to ambient. The solids were filtered and washed sequentially with heptane:xylenes (3:1, 200 ml) and then heptane (200ml). Drying overnight *in vacuo* at 40°C furnished 4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone (110 g, 90% yield). ¹H NMR CDCl₃ 7.43-7.37 (4H, m); 7.22-7.1 (2H, m), 6.97-6.9 (1H, m), 3.05-2.98 (4H, m) and 2.61-2.53 (4H, m).

Example 5

[4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexylidene]-acetonitrile

To a solution of potassium *tert* butoxide (1.0M in THF, 3.20Kg, 3.55mol) in tetrahydrofuran (2.1L) was added diethyl (cyanomethyl)phosphonate (642g, 3.62mol), maintaining the temperature below 5°C. The resulting solution was aged for 2 h and a solution of 4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone (1.07Kg, 2.78mol) (Example 4) in tetrahydrofuran (3.9L) was added. After the reaction was completed, isopropyl acetate (13.1L) and water (26.3L) were

added. The organic layer was washed with brine and then concentrated to 1L. Heptane (10.5L) was added. The resulting solid was filtered, washed with heptane, dried in vacuo at 37°C and then slurried in diethyl ether (5L). Filtration and drying in vacuo afforded 989g (87% yield) of [4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexylidene]acetonitrile.
5 ^1H NMR (CDCl₃) 7.41-7.34 (4H, m), 7.25-7.06 (2H, m), 6.94-6.87 (1H, m), 5.12 (1H, s), 3.05-3.03 (1H, m), 2.92-2.86 (2H, m), 2.54-2.50 (1H, m), and 2.30-2.03 (4H, m).

10 **Example 6**

cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneacetonitrile

A solution of [4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexylidene]acetonitrile (Example 5) (1005g, 2.5mol) in 15 tetrahydrofuran (10.1L) was cooled to -60°C and L-Selectride™ (1.0M in tetrahydrofuran, 2.50Kg, 2.81mol) was added slowly, maintaining the temperature at -60°C. The solution was aged for 60 minutes, warmed to -30°C and treated with 5M sodium hydroxide (285mL) and aqueous hydrogen peroxide (27%) (960mL). Then sodium metabisulphite (95g) was 20 added at -5°C and the resulting mixture was allowed to warm to 15°C. The solution was transferred into a mixture of isopropyl acetate (16.7L), water (15.1L) and sat. brine (3.7L). The organic phase was washed with water:sat. brine (1:1, 14L) and sat. brine (7.3L). The solution was then concentrated to 1.5L and heptane (10L) was added. The resulting solids 25 were filtered and washed with 5% isopropyl acetate in heptane (4L), then dried under vacuum at 37°C to afford *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneacetonitrile, (970g, 95% yield). ^1H NMR CDCl₃ 7.38-7.35 (2H, m), 7.32-7.29 (2H, m), 7.08-7.02 (2H, m), 6.86-6.80 (1H, m), 2.51 (2H, d, *J* = 8 Hz), 2.42-2.45 (4H, m), 2.08-2.03 (1H, m), 1.93-30 1.86 (1H, m) and 1.70-1.61 (4H, m).

Example 7

cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneacetaldehyde

A solution of *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-

5 difluorophenyl)cyclohexaneacetonitrile (Example 6) (967.3g, 2.36mol) in toluene (15.8L) and dichloromethane (4.85L) was cooled to -63°C and diisobutyl aluminium hydride (1.0M in toluene, 2.48Kg, 2.89mol) was added over 60 minutes. Stirring was continued at -60°C for a further 30 minutes before the solution was transferred into 0.75M citric acid (25L).

10 The bi-phasic mixture was stirred overnight at 20°C, the layers were separated and the organic layer was washed with 2M hydrochloric acid (15.8L), 10% sodium bicarbonate (15.8L) and water (15.8L). After evaporation of the solvents, the residue was crystallised from EtOAc/heptane to afford *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneacetaldehyde (922g; 95% yield). ¹H NMR (CD₂Cl₂) 9.65 (1H, t, *J* = 1.7 Hz), 7.32-7.20 (4H, m), 6.98-6.88 (2H, m), 6.85-6.72 (1H, m), 2.57-2.45 (2H, m), 2.45-2.10 (5H, m) and 1.68-1.35 (4H, m).

20 Example 8

cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropanal

A slurry of methoxymethyltriphenylphosphonium chloride (5.14g, 15.0mmol) in toluene (30.0mL) was cooled to -2°C and *t*-BuOK (14.0mL of a 1M THF solution, 14.0mmol) was added. The resulting solution was 25 stirred for 30 min and *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneacetaldehyde (Example 7) (4.13g, 10.0mmol) in toluene (15.0mL) was added. After the reaction was complete, the mixture was quenched with NH₄Cl (10% aq.; 30mL) and the layers separated. The organics were evaporated to dryness and the resultant solids stirred in 30 DMF (45mL) with 1N HCl (7.5mL) at 45°C. After 1 hr, the solution was cooled to 28°C and water (37.5 mL) was added dropwise. The solids were

filtered and washed with DMF:water (33:67, 10mL) and water (10mL). Drying overnight *in vacuo* at 40°C under a nitrogen stream furnished *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropanal (4.04g, 95%). ^1H NMR (CD_2Cl_2) 9.67 (1H, t, J = 1.5 Hz), 7.32-7.20 (4H, m), 5 7.03-6.90 (2H, m), 6.82-6.70 (1H, m), 2.39-2.22 (6H, m), 1.72-1.51 (4H, m) and 1.50-1.30 (3H, m).

Example 9

cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropanal
10 (Alternative route)

(i). Sodium borohydride (97.9g, 2.59mol) was added to a solution of *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)-cyclohexaneacetaldehyde (922g, 2.24mol) (Example 7) in absolute ethanol (6.3L) and toluene (500mL). The reaction was stirred at 4°C for 60 15 minutes before hydrochloric acid (2M, 2.43L) was added. The mixture was allowed to warm to 20°C and stirred until a clear solution was obtained. The latter was transferred into *tert*-butyl methyl ether (15.8L) and water (15.8L), the layers were separated and the organic layer was washed with water (15.8L). The solution was evaporated to dryness, and 2.4L toluene 20 was added to the residue. After the product crystallized, n-heptane (480mL) was added. The slurry was filtered and washed with cold heptane (1L). The solid was dried under vacuum at 38°C to provide *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneethanol (650g). Another 144g was obtained via chromatography of the mother liquors on 25 silica gel, eluting with 30% ethyl acetate in hexanes (combined yield 85%). ^1H NMR CDCl_3 7.37-7.30 (4H, m), 7.10-7.00 (2H, m), 6.86-6.79 (1H, m), 3.73-3.68 (2H, m), 2.42-2.36 (4H, m), 1.78-1.69 (5H, m) and 1.53-1.43 (2H, m).

30 (ii). A solution of *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneethanol (Step (i)) (790g, 1.9mol) in

dichloromethane (7.9L) was cooled to -25°C and triethylamine (387.5ml, 2.47mol) was added followed by methanesulfonyl chloride (176.5 ml, 1.99mol) whilst maintaining the temperature below -25°C. The reaction mixture was aged for 90min. and then quenched into water (7.9L). The 5 layers of the resulting 2-phase mixture were separated. The organic layer was washed with brine (4L), the brine layer extracted with dichloromethane (2L), the combined organic layers dried over sodium sulfate and then concentrated to dryness. The residue was dissolved in dimethyl sulphoxide (7.9L), and potassium cyanide (161g, 2.47mol) was 10 added. The solution was stirred at ambient temperature for 16 hours, warmed to 30°C for 3 hours, and then transferred into a mixture of isopropyl acetate (8L) and water (16L). Further isopropyl acetate (30L) and water (30L) were added. The layers were separated, and the combined organic layers were washed with water (8L). The organic layer 15 was concentrated to dryness, and the product purified by chromatography on silica gel, eluting with dichloromethane, to give *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropionitrile (697g, 87%). ¹H NMR CDCl₃ 7.37-7.29 (4H, m), 7.09-7.00 (2H, m), 6.86-6.79 (1H, m), 2.47-2.37 (6H, m), 1.86-1.81 (2H, m), 1.78-1.72 (3H, m) and 20 1.61-1.52 (2H, m).

(iii). To a solution of *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropionitrile (Step (ii)) (627g, 1.48mol) in dichloromethane (3.14L) and toluene (10.19L) at -60°C under nitrogen 25 was added 1.5M diisobutyl aluminium hydride (1.14Kg, 2.0 mol) over 1 hour. The resulting solution was transferred into 0.75M citric acid solution (25L), and the bi-phasic solution was stirred at room temperature overnight. The layers were separated and the organic phase was washed with 2M hydrochloric acid (17L), water (20L), and brine (1L). 30 Concentration to dryness provided crude *cis*-4-[(4-chlorophenyl)sulfonyl]-4-

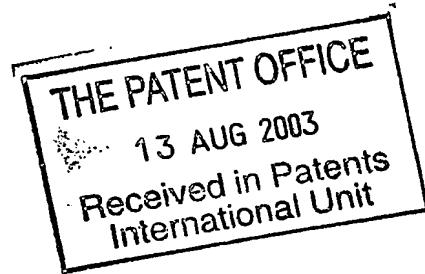
(2,5-difluorophenyl)cyclohexanepropanal as a white solid. ^1H NMR CDCl_3
- as for Example 8

Example 10

5 *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropanoic acid

To a solution of crude *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropanal (Example 9) (650g, 1.52mol) in CH_2Cl_2 (6 L) and H_2O (6L) was added sulfamic acid (215.5g, 2.21mol) followed by slow addition of sodium chlorite (180g in 3.13L H_2O , 2.0 mol) over 30 min. maintaining the internal temperature below 30°C. The phases were separated and the organic layer was washed with an aqueous $\text{Na}_2\text{S}_2\text{O}_5$ solution (157g in 20L H_2O), water (20L) and then dried (Na_2SO_4). The solution was concentrated *in vacuo* and the residue was recrystallised from IPAc/heptane to afford *cis*-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropanoic acid (482g, 74%). ^1H NMR (CDCl_3) 7.37-7.30 (4H, m), 7.09-6.99 (2H, m), 6.85-6.79 (1H, m), 2.42-2.36 (6H, m), 1.85-1.79 (2H, m), 1.73-1.69 (2H, m), 1.63-1.58 (1H, m) and 1.53-1.45 (2H, m).

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